DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of species as compound recited in claim 14 and 17, and addition of claims 14-17 in the reply filed on December 2, 2005 was acknowledged in the non-final office action dated 1/23/06.

Applicant's amendment to claims in the response filed on 5/19/09 has been acknowledged.

Claims 12 and 14-31 are pending.

Applicants have canceled 1-11 and 13.

New claims 23-31 have been added.

Claims 12 and 14-31 are examined on the merit.

Any objections and/or rejections made in the office action dated 2/19/09 and not specifically discussed below in original or modified form here are considered withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 102 (e)

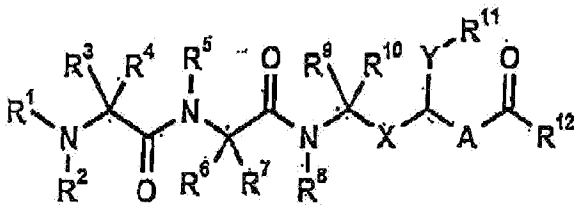
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 23 and 29 remain rejected under 35 U.S.C. 102(e) as being anticipated by Leung (US 2002/0169125 A1). The rejection has been modified to reflect the amendments to claims filed on 5/19/09 and submission of the translation of the foreign priority document. Response to applicant's arguments appears at the end of the reiterated rejection.

Leung anticipates the instant invention under 102(e) because the filing date (March 20, 2002) of Leung precedes the instant application.

In the instant application, applicants claim a compound of general formula U-V-W wherein 'U' refers to formula I as shown below,



(I)

wherein, V is a linker and W is a polymer.

The formula 1 of the instant claim 23, reads on the elected species 'tubulysin'. Claim 23 as recited imply a compound of formula U-V-W wherein the formula I representing the moiety 'U' (tubulysin) conjugated to a polymer in general using a linker of unknown chemical structural characteristics.

Leung discloses a polyanionic polymer conjugated to a drug. The drug being selected from the group that consisted of tubulysin, dolastatin (psuedopeptides) which exhibits cytotoxic properties ([0012] and claim 45). Leung also discloses that the drug can be conjugated to the polyanionic polymer through an indirect linkage (linker) such as a bifunctional spacer [0051] and examples of which include $-[NH\text{-}CHR')_p\text{-}CO]_n-$ wherein R' is side chain of an amino acid, n is

an integer 1 to 10; hydroxy acids; diols; aminothiols; etc., [0052]. This reads on instant claims 23 and 29. Hence Leung anticipates instant invention.

Response to Arguments

Applicants argue that the new claims 23-31 are directed to specific derivatives which are linked to the polymer comprising a PEG with a specific point of attachment. Leung is directed to recombinantly-produced polyanionic polymers.

Applicant's arguments filed 5/19/09 have been fully considered but they are not persuasive. It should be noted that the 102(e) rejection was made on only claims 23 and 29 and not on claims 23-31. The polyanionic polymer and linker of Leung $-[NH\text{-}CHR')_p\text{-}CO]_n-$ wherein the variable R' is selected form the group consisting of diols still reads on the instant new claims 23 and 29 as stated in the rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12 and 14-31 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Leung (US 2002/0169125 A1) as applied to claims 7 and 8 above, in view of Greenwald, 2001, Journal of Controlled Release, 74, 159-171 and further in view of Duncan, 2001, Journal of Controlled Release, 74, 135-146. The rejection has been modified to reflect the amendments made to the claims and addition of new claim. Response to applicant's arguments appears at the end of the rejection.

Leung discloses a polyanionic polymer conjugated to a drug. The drug being selected from the group that consisted of tubulysin, dolastatin (psuedopeptides) which exhibits cytotoxic properties ([0012] and claim 45). Leung also discloses that the drug can be conjugated to the polyanionic polymer through an indirect linkage (linker) such as a bifunctional spacer [0051] and examples of which include $-[NH\text{-}CHR')_p\text{-}CO]_n-$ wherein R' is side chain of an amino acid, n is an integer 1 to 10; hydroxy acids; diols; aminothiols; etc., [0052]. This reads on instant claims 23-27 and 29. Since the linker used in the conjugation use diol and $-[NH\text{-}CHR')_p\text{-}CO]_n-$ linkers that conjugate the drug and the polymer, it reads on the instant claims 14-20 and 28 that recites the variable 'V' being an oxygen atom, or -NH or $-O\text{-}(CR^aR^b)_n\text{-}O-$ which belongs to the genus of diols.

Leung discloses a conjugate of tubulysin (a cytotoxic agent), a linker and a polyanionic polymer, it does not disclose Polyethylene glycol as the polymer.

Greenwald discloses PEG drug conjugates and states that no low molecular weight (<20,000 d) PEG drug conjugates have led to a clinically approved product (abstract). It further states that a renaissance has taken place in the field of higher molecular weight (>20,000 d) conjugates of anticancer drug conjugates and especially employing PEG (40,000 d). This change in the use of higher molecular weight of PEG has improved the plasma circulating half life to 8-9 h in the mouse (abstract). The range in the molecular weight of PEG used, i.e., between 20,000 and 40,000 d for the conjugation to anticancer drugs in Greenwald reference reads on the instant claims 21, 22, 30 and 31.

Greenwald further discloses that "successful application of the PEG prodrug (40,000 d) concept to anticancer agents and the initiation of a clinical trial of PEG-camptothecin by Enzon may be viewed as the beginning of a drug delivery methodology which can be extended to many other classes of compounds: cytokines, blood factors, peptides, antifungals, antibiotics, and immunosuppressive agents, to mention a few".

Duncan discloses that conjugation of anti-tumor dugs to hydrophilic polymers provide an opportunity to solubilize sparingly water soluble drugs, Improve tumor targeting and reduce drug toxicity (Background). Duncan reiterates that the optimum molecular weight of the polymer for conjugation that allows renal elimination is less than 30-40 kDa (Section 2.1 on page 138). Duncan also discloses several polymer conjugated drugs, for example polyglutamic acid-paclitaxel which is a polyanionic polymer conjugated drug (as also disclosed by Leung) in phase I/II testing. Instant claim 7 is drawn to a polymer conjugated tubulysin and instant claim 12 and 13 are drawn to method of treating patient suffering cancer. Since Duncan discloses polyanionic conjugated drug in the clinical trials, it reads on the instant claims 12 and 13.

It would have obvious to one of ordinary skill in the art to combine the afore-discussed teachings of Leung, Greenwald and Duncan to arrive at the instant invention. It would have been obvious because, the problem that is solved by the instant invention is the conjugation of tubulysin with a polymer using a linker molecule. This aspect of the invention was well recognized in the Leung and the reference discloses such a conjugate of tubulysin with polyanionic polymer. Duncan teaches that polyanionic conjugated paclitaxel in clinical trials and Greenwald discloses that anticancer drugs conjugated to higher molecular weight PEG extends half life in plasma. Although the cited references do not teach the conjugation of tubulysin with PEG, the motivation to do so comes from Greenwald. Greenwald as mentioned earlier further states that "successful application of the PEG prodrug (40,000 d) concept to anticancer agents and the initiation of a clinical trial of PEG-camptothecin by Enzon may be viewed as the beginning of a drug delivery methodology which can be extended to many other classes of compounds: cytokines, blood factors, peptides, antifungals, antibiotics, and immunosuppressive agents, to mention a few". This would be a strong motivation for one of ordinary skill in the art to conjugate the tubulysin to PEG to increase the half-life in plasma and lower the toxicity as taught by Duncan and Greenwald. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

1. Applicants argue that the new claims 23-31 are drawn to compounds bearing the 'same base formula' and are directed to specific derivatives which are linked to a polymer 'comprising' a PEG (emphasis added by the office). Applicants also state that Leung discloses tubulysin among a list of possible drugs and not disclose tubulysin linked to such a polyanionic polymer. Applicants also state that nothing in Leung describes the reduction of toxicity of a drug using the specific derivatives as claimed in the instant application.

2. Applicants reiterate some of the earlier arguments that have been addressed in the earlier office action dated 10/29/08 (pages 5-7).

3. Applicants submit a copy of the Schluep (2009, Clin. Cancer Res, 15, 181-189) as evidence to show further experimental data for tubulysin derivative linked to a polymer comprising PEG. Applicants also state that the declaration in the form of poster submitted earlier combined with the teachings of Schluep infer that the cyclodextrin-PEG-polymer conjugates of tubulysin show high antiproliferative activity in human cancer cells and are significantly less toxic than tubulysin.

4. Applicants argue that Duncan does not disclose conjugates comprising a tubulysin and a polymer comprising a PEG. Like Leung and Greenwald, Duncan cannot render the present invention obvious.

Applicant's arguments filed 5/19/09 have been fully considered but they are not persuasive.

1. Applicants acknowledge that the new claims are drawn to the 'same base formula' and are directed to specific derivatives which are linked to a polymer 'comprising' a PEG (emphasis added by the office). Hence the new claims are drawn to the same chemical compounds and hence the rejection of record applies to the newly submitted claims. Applicant's argument that Leung discloses tubulysin among a list of possible drug compounds conjugated to polyanionic polymer and does not disclose that the tubulysin linked to such a polymer is not persuasive, because, Leung teaches the concept of attaching drug molecules to polyanionic polymers that uses a bifunctional linker like a diol. This clearly reads on the instant claims as stated in the rejection.

2. The issues raised by the applicants have been answered in the earlier office action dated 10/29/08 (pages 5-7).

3. Applicant's submit a copy of a publication that is post-dated to the instant invention. A posted publication is used to show scientific truism (see MPEP Section 2123) that states "[I]n certain circumstances, references cited to show a universal fact need not be available as prior art before applicant's filing date. In re Wilson, 311 F.2d 266, 135 USPQ 442 (CCPA 1962). Such facts include the characteristics and properties of a material or a scientific truism". By referring to a post-dated article applicants' acknowledge that conjugation of toxic drugs to PEG improves the activity of the drug and lowers the toxicity of the drug that are well known in the art.

4. If Duncan has disclosed a conjugate of tubulysin with a polymer comprising PEG, the rejection would have been under anticipation and not under obviousness.

Double Patenting

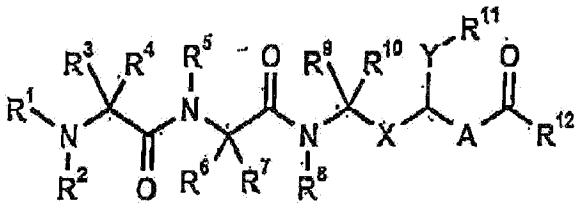
The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The rejection has been modified to reflect the claim amendments made in the instant application. Response to applicant's arguments appears at the end of the rejection.

Claim 23 remains provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19-32 of copending Application No. 10520793 in view of Leung (US 2002/0169125 A1). Instant claim 23 is drawn to a compound of formula U-V-W wherein U is represented by the formula,



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wherein, V is a linker and W is a polymer.

Claim 19-32 of the copending Application No. 10520793 recites compound of formula I shown above.

The invention in copending application 10520793 does not disclose a conjugate U-V-W wherein the variable 'U' is the compound of formula I.

However, Leung discloses a polyanionic polymer conjugated to a drug. The drug being selected from the group that consisted of tubulysin, dolastatin (psuedopeptides) which exhibits cytotoxic properties ([0012] and claim 45). Leung also discloses that the drug can be conjugated to the polyanionic polymer through an indirect linkage (linker) such as a bifunctional spacer [0051].

One of ordinary skill in the art would combine the teachings of the copending Application No. 10520793 with Leung to arrive at the instant invention. Because, Leung teaches conjugation of tubulysin a species of formula I of instant application with a polyanionic polymer via a linker. One would be motivated to do so given the fact that copending application teaches the generic formula of compound I and Leung discloses a conjugate of a species of formula I with a polymer using a linker. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject

matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

This is a provisional obviousness-type double patenting rejection.

Claim 23 directed to an invention not patentably distinct from claims 19-32 of commonly assigned 10520793. Specifically, as illustrated above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned instant application and 10520793, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly

assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Response to Arguments

Applicants argue that cancellation of claim 7 in the instant application renders the double patenting moot.

Applicant's arguments filed 5/19/09 have been fully considered but they are not persuasive. It should be noted that claim 23 of the instant application recites claims that are drawn to the 'same base formula' and are directed to specific derivatives which are linked to a polymer 'comprising' a PEG as acknowledged by the applicants. Hence a double patenting rejection on the new claim 23 is proper and is maintained.

Conclusion

Applicant's amendment to claims does not overcome the pending rejection as illustrated above.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Satyanarayana R Gudibande/
Examiner, Art Unit 1654

/Andrew D Kosar/
Primary Examiner, Art Unit 1654